EPIDEMIOLOGY, STATISTICS and PSYCHOSOMATIC NO. 347

COMMITTEE:
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Dr. Cattell
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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 12, 1962

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1. Name of Investigator: ARNOLD R. KAPLAN, PH.D.

2. Title: Director, Laboratory of Medical Genetics
Cleveland Psychiatric Institute and Hospital

3. Institution and Address: Psychiatric Research Foundation of Cleveland
1708 Aiken Avenue
Cleveland 9, Ohio
(Executive Director: Edward N. Hinko, M. D.)

4. Project or Subject: EXAMINATION OF CORRELATIONS BETWEEN TASTE THRESHOLDS (for QUININE and 6-n-propylthiouracil) and HABITUAL (i.e., smoking), PHYSIOLOGICAL and PATHOLOGICAL VARIABLES.

5. Detailed plan of procedure:

A. SPECIFIC AIMS: - The specific aims of the proposed research project include clarification of the constitutional basis and significance of correlations occurring between taste threshold categories, as defined for quinine and 6-n-propylthiouracil, and the following variables:

(1) habitual -- i. e., smoking habits;
(2) physiological -- i. e., metabolic rates, blood pepsinogen levels;
(3) pathological predispositions -- i. e., to gastritis, gastric ulcer, duodenal ulcer, coronary disease, thyroid disease, migraine, etc.

B. METHODOLOGY: - Taste thresholds will be determined in all subjects for quinine sulfate (U.S.P. crystals, Mallinkrodt) and 6-n-propylthiouracil (Nutritional Biochemical Corp.). Normal subjects and patients in the relevant pathological categories will be tested with a modification of the Harris-Kalmus double-blank placebo procedure and final sorting-out technique. The basic method involves 20 concentrations (ranging from 3.66×10^{-7} to 3.84×10^{-1}) each of which is double the concentration of the next-lower solution. Previously-published studies of taste threshold have been based on defective methodology. The following refinements now make possible an accurate genetic study of the taste threshold phenomena:

(1) Threshold determinations to fractional powers of 0.1. We are now utilizing

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a refinement of the Harris-Kalmus procedure which involves not only doubling concentrations, but also fractional powers of the 0.1. between the primary concentrations. Our technique involves, therefor, determination of taste threshold to an accuracy of one decimal point beyond that employed in the original Harris-Kalmus procedure. This refinement is important because certain thresholds, and certain combinations of 6-n-propylthiouracil thresholds and quinine thresholds, are apparently genetic entities. The genetic mechanisms involved can only be elucidated, however, if the more exact thresholds are determined. For example, with an unrefined Harris-Kalmus procedure, a subject with an actual threshold of '12.3' would be categorized as '13.' Since the threshold range between '12' and '13' appears to include a critical dichotomy between genetic entities, the previously-used techniques are unsuitable for accurate genetic determinations.

(2) Previous use of phenylthiourea ('P.T.C.') instead of 6-n-propylthiouracil meant that taste measurements were based on a very odorous and toxic compound -- and the apparent distributions of taste threshold categories were distorted by the uncontrolled variable of differential olfactory sensitivities to the compound. Thus, previous studies (e. g., by Merton) included mating pairs of 'nontasters' who produced 'taster' offspring -- in contradiction to the classical genetic hypothesis that the factor for 'nontaster' is transmitted as a simple Mendelian recessive. The use of 6-n-propylthiouracil is also justified by its superior potency, which facilitates more reliable differentiation between the different threshold categories; and by the fact that 6-n-propylthiouracil is the least toxic of the thioureas.

(3) Sequence in determination of the taste thresholds. Leguebe and Kalmus each tested the taste thresholds for phenylthiourea and quinine, in that consecutive order. We have found that the occurrence of a strong affinity for the thiourea compound blunts, for several hours, the taste thresholds for subsequently-tested compounds. Only a testing sequence in which the quinine threshold is determined first and the thiourea (in our procedure, 6-n-propylthiouracil) afterwards, provides accurate threshold determinations for both compounds.

Smoking data will be based on the standard questionaire of the Tobacco Industry Research Committee. The utilization of the standard questionaire will facilitate replication by other investigators.

Blood pepsinogen levels will be determined by standard procedures, and correlated with the other variables being investigated. Mirsky et al. have shown that patients with duodenal ulcer histories have high blood pepsinogen levels compared to the general population. Our preliminary findings of correlations between taste insensitivity (i. e., high threshold), ulcer history and other variables, suggest the possibility of an etiological relationship between the taste-thresholds (and relevant genetic factors) and blood pepsinogen levels.

Data relevant to body type will also be evaluated. We will determine heights and weights of the subjects -- two easily-accessible categories of data, from which the subjects' body surfaces may be calculated. Body surface, rather than 'Sheldonian' or 'Kretchmerian' categories, is related to metabolic rate -- and this data will be investigated for correlations with the above variables. The importance of considering metabolic rate (indirectly, from body surface calculations) is indicated by the data which indicate a correlation between taste threshold and thyroid activity. We have found that hyperthyroid patients tend to be insensitive tasters -- i. e., nine of the subjects in a pilot group of 12 tested hyperthyroid patients could not taste even the uppermost concentrations of quinine and 6-n-propylthiouracil. Since the latter substance is an antithyroid drug, and hyperthyroid patients (with diagnoses of thyrotoxicosis or toxic nodular goiter) cannot taste the saturated solution of an antithyroid drug, taste threshold for this drug is related to metabolic rate. A significantly higher proportion of insensitive ("non-") tasters has been found in hyperthyroid subjects than in the general population. These observations gain

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significance when considered in the light of data reported by Kitchen et al., who observed a tendency to "taste blindness" (i. e., insensitivity) in patients with multi-adematous goitre, both toxic and non-toxic, and in those with toxic diffuse goitre; and data reported by Shepard and Gartler, on parents of cretins, which indicate a similar correlation between taste sensitivity and thyroid activity. Based on the above observations, we would expect to find positive correlations, on the one hand, between high thyroid activity, taster insensitivity and heavy smoking -- and, on the other hand, between low thyroid activity, taster sensitivity and non-smoking. The pathologies of which predispositions are correlated with taste insensitivity may be primarily related to metabolic variables, as may be the variables of taste sensitivity and smoking habits.

C. PREVIOUS FINDINGS AND OTHER RELEVANT MATERIAL: - Preliminary pilot studies indicate that subjects who are extremely insensitive to taste for 6-n-propylthiouracil ('threshold levels 13-14') always fall in the range of low taste sensitivity for quinine ('threshold levels of 7 and above'), and include a significantly high proportion of individuals with positive histories for gastritis, ulcers and migraine. Our studies have also shown that drug reactivity (i.e., drug sensitivity) is correlated with taste thresholds for quinine and 6-n-propylthiouracil -- as are food dislikes and smoking habits. Therefor, we consider it reasonable to examine the genetic factors relevant to constitutional differences correlated with the above variables. To date, there has been no 'clean-cut' study of the genetics of taste thresholds for 6-n-propylthiouracil and the relevant involvement of taste thresholds for quinine.

Krut, Perrin and Bronte-Stewart recently reported finding a significant correlation between smoking habits and high taste thresholds for quinine. They found that only the taste threshold for the bitter compound is correlated with smoking habits -- and that taste thresholds for sweetness, saltiness and acidity have no correlations with smoking habits. Our own data indicate that smoking habits and food dislikes are both apparently related to taste thresholds for the bitter compounds (only). Our investigations confirm the above observations reported by Krut et al. -- whose methodology, incidentally, involved placement of a drop of test solution with a pipette on the middle of the tongue. They tested for taste thresholds for phenylthiourea as well as for quinine, but found no correlation with the former. Their technique (of placing one drop of phenylthiourea solution in the middle of the tongue) does not facilitate taste detection in many cases, however, and the methodology is defective for determination of phenylthiourea taste threshold. Two or three seconds of lag time are required for tasting phenylthiourea -- and in addition, for taste detection, the solution must flow all over the tongue and especially over the root and sides. Their studies of taste thresholds for phenylthiourea are meaningless due to the methodological defects, but their studies with quinine provided accurate and reproducable results -- because taste testing for quinine does not require lag time and does not require contact on the deep portion of the tongue. We have preliminary evidence (based on 137 healthy subjects) which support the findings of Krut et al. that 'sensitive tasters' contain significantly lower proportions of 'heavy smokers' than do the relatively 'insensitive tasters.' Preliminary data also indicate correlations between taste thresholds (for quinine and 6-n-propylthiouracil) and morbidity rates for several pathologies. A positive correlation has also been found between high taste sensitivity (i.e., low taste threshold) for the bitter compounds and extent of food dislikes. No correlations have been found with taste thresholds for sweetness, saltiness and acid.

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D. REFERENCES

Harris, H. and H. Kalmus. 1949. Ann. Eugen., 15:24.
Kalmus, H. 1958. Ann. Hum. Genetics, 22:222.

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REFERENCES - Continued

Kitchen, F. D., et al. 1959. Brit. Med. J., 1: 1069.
Krut, L. H., M. J. Perrin and B. Bronte-Stewart. 1961. Brit. Med. J., 1;384.
Leguebe, A. 1960. Bull. Inst. Royal des Sciences Nat. de Belgique, 36:1.
Merton, B. B. 1958. Acta Genet. Statist. Med., 8:114.
Shepard, T. H. and S. M. Gartler. 1960. Science, 131:929.

6. Budget Plan: (First Year)

a.	Salaries	$6,600.00
b.	Expendable Supplies	1,500.00
c.	Permanent Equipment	1,190.00
d.	Overhead (15% of a,b,e)	1,552.00
e.	Other	2,250.00
	TOTAL	$13,092.00

7. Anticipated Duration of Work: THREE YEARS
(See 'Additional Requirements' for suggested second and third year budgets).

8. Facilities and Staff Available: The principle investigators are Dr. Arnold R. Kaplan, Director of the Laboratory of Medical Genetics, and Mrs. Mary Wilkinson Fox, Statistics Consultant and Research Associate, at the Cleveland Psychiatric Institute and Hospital; Dr. Roland Fischer, Senior Research Biochemist, and Mrs. Frances Griffin, Research Associate, at the Columbus Psychiatric Institute, and Ohio State University Medical School. Facilities available include the research and clinical facilities of the respective institutions. Agreements for collaboration have been made with the chiefs and staff members of the Departments of Psychiatry, Psychosomatic Medicine, Medicine, Pharmacology and Physiological Chemistry at the Ohio State University Medical School -- and with the director of the serology laboratory at the Cleveland Metropolitan General Hospital.

9. Additional Requirements: Budget Plan - Second Year and Third Year.

		Second Year	Third Year
a.		$6,700.00	$6,800.00
b.		500.00	400.00
c.		150.00	- -
d.		1,357.00	1,290.00
e.		1,850.00	1,400.00
	TOTALS	$10,557.00	9,890.00

10. Additional Information (including relation of work to other projects and other sources of supply)

The named applicant investigators are staff members of their respective (state) institutions and draw full-time salaries therefrom.

Other projects, in progress and planned (and for which some pilot data have already been collected) which are related to the present proposal are as follows:

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10. Additional Information -(Cont'd)

(1) We are planning a concomitant study to test the possibility that certain personality types, as defined by quantifiable personality tests, may be correlated with certain thresholds and/or threshold combinations for tasting 6-n-propylthiouracil and quinine. If the pilot studies should yield significant data, we would include the personality tests in the present project.

(2) In conjunction with the above study, we are planning to investigate the occurrence of possible personality correlates with the dichotomy separating subjects into categories of 'learners' and 'nonlearners' of greater taste sensitivity.

(3) Studies are continuing, investigating the relationship between drug (psilocybin) reactivity of 'normal' subjects as related to taste thresholds for quinine and 6-n-propylthiouracil.

(4) Studies are continuing, investigating the relationship between taste threshold for quinine and 6-n-propylthiouracil in uncategorized mental patients and the setting-in of Parkinsonism with progressively-increased chlorpromazine dosages.

(5) Studies are planned to determine genetic linkage between the loci for the 'taster' factor, blood types and other genetic markers.

(6) Studies are planned, to investigate the taste threshold phenomena in twin-family pedigrees.

Signature ARNOLD R. KAPLAN
Director of Project

EDMOND N. HINKER, M. D.
Business Officer of Institution

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